

plasma and blood transfusions, infections, autoimmune disorders, pregnancies, malignancies, and antibiotics [2-4]. We report the first case of an acquired factor V inhibitor in the setting of HIV infection.

A 32-year-old man with HIV infection presented 10 days prior to admission with fever and weight loss for 2 months and diffuse lymphadenopathy. His hemoglobin (Hb) and platelet count were normal with a CD4 count of 220/ μ l (nl 410-1,840) and a CD8 count of 1730/ μ l (nl 270-870). On admission, he had a temperature of 100.5°F, and a Hb of 82 g/L (nl 120-150), platelet count of 7×10^9 /L (nl 150-450), reticulocyte % of 3.9 (nl 0.5-1.5), and LDH of 1,725 U/L (nl 297-611). Prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT) were normal. A direct Coomb's antibody test was negative. The peripheral smear contained schistocytes and large platelets. His mental status, creatinine, and urinalysis were normal. A diagnosis of thrombotic thrombocytopenic purpura (TTP) was made and plasma exchange was begun. After initial improvement (Fig. 1), the platelet count decreased. A bone marrow biopsy showed plasmacytosis and increased megakaryocytes. Elevated antiplatelet antibodies [IgM 19.7% (nl 2.2-7.2) and IgG 37.4% (nl 2.1-12.1)] suggested a diagnosis of AIT. Plasma exchange was discontinued, and intravenous immunoglobulin (IVIG) was started. A cervical lymph node showed Kaposi sarcoma (KS), and an abdominal CT scan showed lymphadenopathy and splenomegaly. His thrombocytopenia was thought due to HIV-associated AIT and splenomegaly-KS, so he was treated with azidothymidine and vincristine plus interferon- α (IFN- α). A preoperative evaluation for a splenectomy revealed a PT of 21.9 sec (nl 11.1-12.9), INR of 4.3 (nl ratio 1.0), and PTT of 61.2 sec (nl 20.0-33.5). These did not correct with vitamin K or fresh frozen plasma. His measured factor II activity was 64% (nl 83-126), factor V was 12% (nl 66-152), factor VII was 59% (nl 66-156) and factor X was 75% (nl 65-142). A factor V mixing study was 9% (nl 85%) and factor V 50:50 mixed study was 28% (nl 47%), demonstrating the presence of a factor V inhibitor. Splenectomy was postponed, and on hospital day 17 his platelet count increased. He was discharged home with a platelet count of 131×10^9 /L. His coagulation indices normalized 1 month later while receiving weekly vincristine.

During plasma exchange, he was exposed to 156 units of foreign factors that likely served as the antigenic stimulus to develop the inhibitor. Patients with coagulation factor inhibitors have been treated with FFP, cyclophosphamide, and prednisolone; platelets are used specifically for factor V inhibitors [5]. Specific therapy was not instituted because the patient was asymptomatic, the risk of further immunosuppression, and the possibility his inhibitor might disappear spontaneously. His asymptomatic course suggests that expectant management may be appropriate.

REFERENCES

1. Sande MA, Volberding PA (eds): The Medical Management of AIDS, 2nd ed., pp 33. Philadelphia, PA: W.B. Saunders Company, 1990.
2. Brandt JT, Britton A, Kraut E: A Spontaneous factor V inhibitor with unexpected laboratory features. *Arch Pathol Lab Med* 110:224-227, 1986.
3. Nesheim ME, Nichols WL, Cole TL, Houston JG, Schenk RB, Mann KG, Bowie EJJW: Isolation and study of an acquired inhibitor of human coagulation factor V. *J Clin Invest* 77:405-415, 1986.
4. Chediak J, Ashenbush JB, Garlick I, Dessler RK: Successful management of bleeding in a patient with factor V inhibitor by platelet transfusions. *Blood* 56:835-841, 1980.
5. Smid WM, de Wolf JTM, Nijland JH, Bom VJJ, van der Meer: Severe bleeding caused by an inhibitor to coagulation factor V: A case report. *Blood Coag Fibrin* 5:133-137, 1994.

L.A. BRICKNER
K.A. SCANNELL

Department of Medicine, Kaiser Permanente
Oakland, California

M.A. SAHOD

Coagulation Center, Summit Medical Center,
Oakland, California

Leukopenia, Thrombocytopenia, and Acute Autoimmune Hemolytic Anemia Associated With an Unusual (Type 2/4) Hodgkin's Disease: Case Report

To the Editor: The association of autoimmune hemolytic anemia (AIHA) and Hodgkin disease (HD) was first described in 1967 [1]. The reported frequency of this association ranges from 0.2% [2] to 1.7% [3]. Autoimmune neutropenia is extremely uncommon in HD [4,5], in contrast to immune thrombocytopenia (ITP) which is more frequent in HD (1% to 2%) than in the general population [2]. We describe here a new presentation of HD, associating AIHA, ITP and leukopenia.

A 24-year-old woman was admitted for asthenia, jaundice, and fever. Physical examination discovered cervical adenopathies, splenomegaly, and hepatomegaly. Computed tomography (CT) detected mediastinal, celiomesenteric and lomboarctic adenopathies. Hemoglobin level was 4 g/dl; platelets, 71,000/ mm^3 , and white blood cells (WBC), 1,300/ mm^3 , with 74% neutrophils, 14% lymphocytes, and 12% monocytes. The haptoglobin level was 0.06 g/L (normal value 0.54-1.43), total bilirubin was 65 μ mol/L (normal value <20), mainly unconjugated (41 μ mol/L), lactate dehydrogenase (LDH) was 411 IU/L (normal value <330). The reticulocyte count was 394,000/ mm^3 . The direct and indirect Coombs tests were positive for IgG, but not for complement. Fibrinogen was 3 g/dl, C-reactive protein (CRP) was 24 mg/L (normal value <6), coagulation tests were normal; and no schistocytes were observed. The human immunodeficiency virus (HIV) test was negative. Hemoglobin electrophoresis was normal. The serum electrophoresis showed polyclonal immunoglobulin increase, but without any monoclonal component on immunoelectrophoresis. The medullogram was hypercellular, showing an important erythrocytic hyperplasia (61%), a rich granulocytic lineage (28%), and many megakaryocytes. Osteomedullary biopsy revealed foci of neoplastic involvement containing few atypical large cells surrounded by fibrosis, suggesting HD lesions. A large cervical lymph node was excised and histological analysis (Fig. 1) showed replacement of the normal node architecture by widespread fibrosis containing a few nodular nests of small lymphocytes and scattered Reed-Sternberg cells (R-SC) of classic immunophenotype (CD15+ and CD30+, CD3-). The lymphocytic cellular component exhibited marked plasmacytoid features (Fig. 1C) with a polyclonal pattern of intracytoplasmic Ig light chain immunodetection. The diagnosis of HD was done, as an intermediate form between type 2 (nodular sclerosis) and type 4 (lymphocyte depleted, fibrotic). Acute intravascular AIHA lead to corticosteroid treatment (2 mg/kg/day) that had no results after 10 days. The severity of anemia prompted plasmapheresis, which was partly successful; the platelets increased to 152,000/ mm^3 , WBC to 6,100/ mm^3 , and hemoglobin to 6.5 g/dl. Unfortunately, this response was only transient, and finally, splenectomy was performed, that obtained only transient cessation of hemolysis, with little effect on platelet and leukocyte numeration. Histological examination of the spleen found HD lesions, in association with myeloid metaplasia. A chemotherapy (MOPP regimen) was initiated, but the patient died on day 10 of sepsis and disease progression.

Severe pancytopenia at diagnosis rised the problem of chemotherapy beginning. The attempts to resolve the autoimmune process (corticosteroids, plasmapheresis, splenectomy) gave only mild and transient results, leading to chemotherapy despite the hematological conditions. Although the issue of this patient was unfavourable, salvage chemotherapy was the only solution since the prognosis of cytopenias seems to be related only to the status of the underlying HD [2].

The autoimmune origin of the hemolytic anemia is proven by the positive Coombs test. The peripheral origin of thrombocytopenia is supported by the presence of numerous megakaryocytes in the marrow, and its immunological mechanism was suggested in the absence of other causes of platelet destruction (e.g., viral infection, disseminated intravascular coagulation). Although hypersplenism could have participated, splenectomy did not improve the thrombocytopenia. The peripheral origin of neutropenia was also most

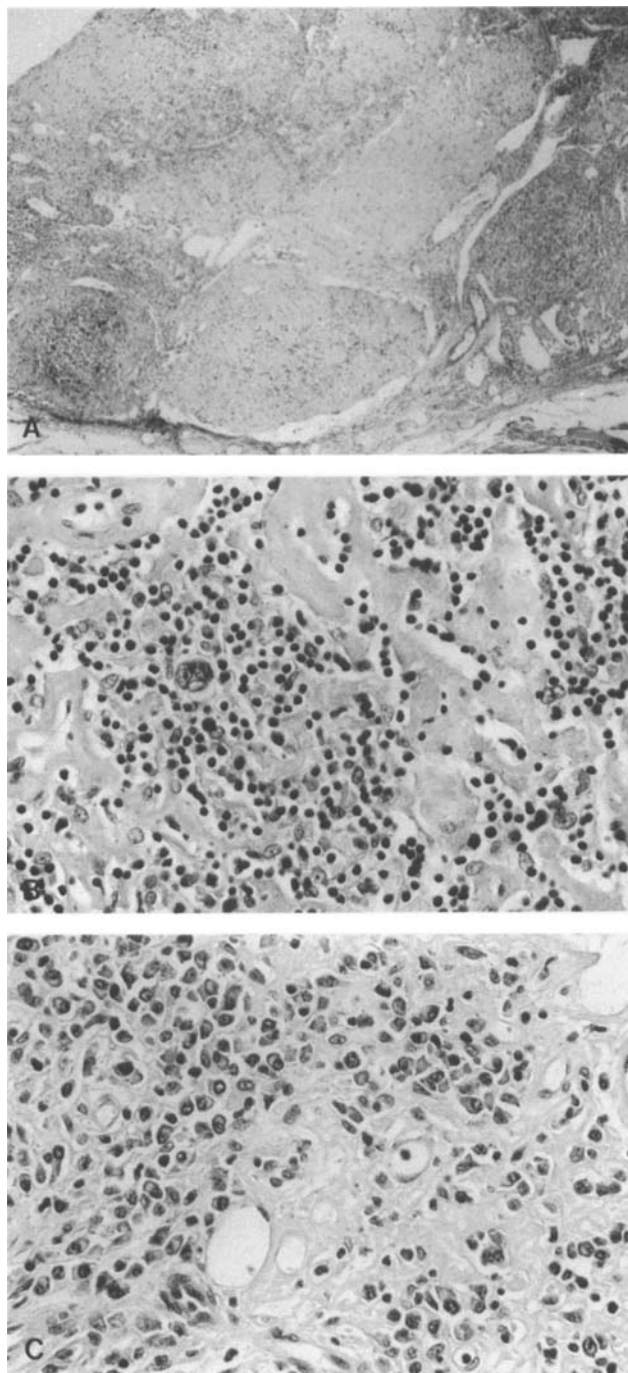


Fig. 1. Biopsy of a cervical node. **A:** Low-power view showing the nodular pattern associated with widespread sclerosis. **B:** Typical Reed-Sternberg cell among a few lymphocytes and fibrotic bands. **C:** Sheets of plasma cells among collagenous deposits.

probable, since medullogram and bone marrow biopsy were rich and displayed normal granulocytic differentiation. We did not perform a search for antineutrophil or antiplatelet antibodies, but the favourable response to plasmapheresis suggested the involvement of circulating autoantibodies, although we cannot exclude other soluble factors.

Auto antibodies could be directly produced by tumour cells, by nonspecific tumoral infiltrates, or being related to the immune regulatory phenome-

non directed against HD. The absence of a monoclonal component in serum or urine, together with the absence of monotypic immunoglobulin detection in tumoral cells argue against the first hypothesis. Although its specificity was not determined in our patient, the antibody associated with AIHA in patients with HD has been identified as an anti transition (Iⁱ) antigen antibody [6]. This antigen occurs during the transition from i to I antigen in the development of the erythrocyte Ii antigen system, that also exists on myeloid cells [7]. A modified Ii antigen expression or association on the surface of tumoral cells could lead to abnormal antibody synthesis. Finally, a dysregulated Ig production by normal cells infiltrating the tumour would be in line with the importance of the plasmacytoid infiltrate observed in our patient and in at least two other cases [3,8].

We and others [9,10] have previously shown that R-SC are capable of modulating their environment by producing a number of cytokines, including interleukin-6 (IL-6), which could account for the polyclonal reactive plasma cell hyperplasia observed in our case. It is noteworthy indeed that histological analysis showed intermingled features of diffuse fibrosis (HD type 4) and nodular sclerosis (HD type 2), suggesting a sequential link between the two forms of the disease, an association not previously reported. Finally, the pathogenesis of HD cases with autoimmune manifestations could be related to a complex cascade of cytokine signals, in particular IL-6, orchestrated by R-SC, with the functional properties of these cells not elucidated.

REFERENCES

1. Eisner E, Ley AB, Mayer K: Coombs' positive hemolytic anemia in Hodgkin's disease. *Ann Intern Med* 66:258, 1967.
2. Xiros N, Binder T, Anger B, Bohlke J, Heimpel H: Idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia in Hodgkin's disease. *Eur J Haematol* 40:437, 1988.
3. Andrieu JM, Youinou P, Marcelli A: Anémie hémolytique autoimmune associée à la maladie de Hodgkin. Caractéristiques, pronostic et incidence. [Autoimmune haemolytic anaemia associated with Hodgkin's disease. Characteristics, prognosis and incidence (author's transl)]. *Nouv Presse Med* 10:2951, 1981.
4. Weitberg AB, Harmon DC: Auto immune neutropenia, hemolytic anemia, and reticulocytopenia in Hodgkin's disease. *Ann Intern Med* 100:702, 1984.
5. Hunter JD, Logue GL, Joyner JT: Auto immune neutropenia in Hodgkin's disease. *Arch Intern Med* 142:386, 1982.
6. Garraty G, Petz LD, Wallerstein RO, Fudenberg HH: Auto immune hemolytic anemia in Hodgkin's disease associated with anti-Iⁱ. *Transfusion* 14:226, 1974.
7. Moore JO, Logue GL: I and i antigens on normal and leukemic leukocytes. *Cancer* 42:140, 1978.
8. Levine AM, Thornton P, Forman SJ, Van Hale P, Holdorf D, Rouault CL, Poward S, Feinstein DI, Lukes RJ: Positive Coombs test in Hodgkin's disease: significance and implication. *Blood* 55:607, 1980.
9. Xerri L, Birg F, Guigou V, Bouabdallah R, Poizat-Martin I, Hassoun J: In situ expression of the IL-1 α and TNF- α genes by Reed-Sternberg cells in Hodgkin's disease. *Int J Cancer* 50:689, 1991.
10. Haluska FG, Brufsky AM, Canellos GP: The cellular biology of the Reed-Sternberg cell. *Blood* 84:1005, 1994.

RÉGIS T. COSTELLO
LUC XERRI
REDA BOUABDALLAH
JEAN-ALBERT GASTAUT
DANIELE SAINTY

*Departments of Hematology, Biology, and Anatomic-Pathology,
Institut Paoli-Calmettes, Marseille, France*

Thrombotic Thrombocytopenic Purpura and 17 β -Estradiol Transdermal Skin Patch

To the Editor: Thrombotic thrombocytopenic purpura (TTP) is an uncommon disorder characterised by consumptive thrombocytopenia, microangio-